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<p>(21) International Application Number: PCT/EP97/00135</p> <p>(22) International Filing Date: 21 January 1997 (21.01.97)</p> <p>(30) Priority Data: 60/011,048 25 January 1996 (25.01.96) US</p> <p>(71) Applicant: F.HOFFMANN-LA ROCHE AG [CH/CH]; Grenzacherstrasse 124, CH-4070 Basle (CH).</p> <p>(72) Inventors: BERGER, Jacob; 12135 Dawn Lane, Los Altos Hills, CA 94022 (US). FLIPPIN, Lee, Allen; 17659 Skyline Boulevard, Woodside, CA 94062 (US). HUNTER, John, Cureton; 12077 Carol Lane, Saratoga, CA 95070 (US). LOUGHHEAD, David, Garrett; 505 Vannier Drive, Belmont, CA 94002 (US). WEIKERT, Robert, James; 16200 Skyline Boulevard, Woodside, CA 94062 (US).</p> <p>(74) Agent: MAHE, Jean; Grenzacherstrasse 124, CH-4070 Basle (CH).</p>		<p>(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, HU, IL, IS, JP, KP, KR, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report.</p>
<p>(54) Title: (2-DIMETHYLPHENOXY-1-METHYLETHYL) ETHYLAMINE</p> <p>(57) Abstract</p> <p>This invention relates to a compound of formula (I) namely [2-(2,6-dimethylphenoxy)-1-methylethyl]ethylamine and its pharmaceutically acceptable salts thereof, to racemic and non-racemic mixtures thereof, and in particular to its (R)-enantiomer. The compound of Formula (I) is a sodium channel blocker, and thus exhibits useful pharmacological properties, especially utility for the alleviation of neuropathic pain.</p> <div data-bbox="1015 1570 1627 1785"><p style="text-align: right;">(I)</p></div>		

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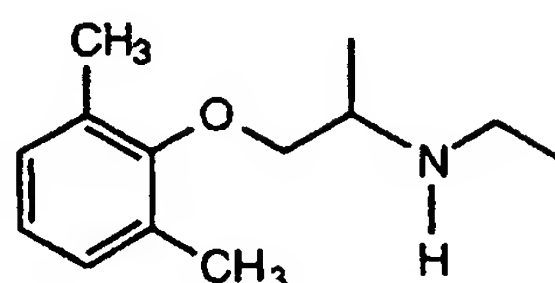
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(2-Dimethylphenoxy-1-methylethyl)ethylamine

This invention relates to a compound of the Formula I:



I

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15
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namely [2-(2,6-dimethylphenoxy)-1-methylethyl]ethylamine and its pharmaceutically acceptable salts thereof, to racemic and non-racemic mixtures thereof, and in particular to its (R)-enantiomer. The compound of Formula I is a sodium channel blocker, and thus exhibits useful pharmacological properties, especially utility for the alleviation of neuropathic pain.

15
20
Neuropathic pain can be described as pain associated with damage or permanent alteration of the peripheral or central nervous system. Clinical manifestations of neuropathic pain include a sensation of burning or electric shock, feelings of bodily distortion, allodynia and hyperpathia.

25
Sodium channel-blocking agents have been reported to be effective in the treatment of various disease states. They are in particular useful as local anesthetics, and in the treatment of arrhythmia. It has also been reported for many years that sodium channel-blocking agents may be useful in the treatment of pain, including neuropathic pain; see, for example, Tanelian et al., *Pain Forum.*, 4(2), 75-80, (1995). There is evidence that sodium

channel-blocking agents selectively suppress ectopic
neural firing in injured nerves, and it is via this
mechanism that they are believed to be useful for
relieving pain. However, studies carried out on well known
5 sodium channel-blocking agents, for example carbamazepine,
phenytoin, lidocaine, mexiletine, and the like, indicate
that these agents are not very effective for the treatment
of neuropathic pain conditions at moderate dose levels,
and that even at these moderate dose levels they are
10 associated with a range of undesirable side effects, such
as vertigo, nausea, somnolence, tremor, slurred speech,
etc.

Numerous sodium channel-blocking agents have been
15 disclosed in the patent and non-patent literature. For
example, mexiletine (1-(2,6-dimethylphenoxy)-2-
propanamine), a well-known sodium channel-blocking agent
and antiarrhythmic, is disclosed in U.S. Patent Nos.
3,659,019, 3,954,872, and 4,031,244 (Köppe et al.).

20 Two Chinese references, *Yaoxue Xuebao*, 19(9), 656-659
(1984) and *Acta Pharmaceutica Sinica*, 25(2), 150-153
(1990), disclose mexiletine derivatives and analogues,
their physical properties, and physiological activities.
25 In particular, the references include mexiletine
derivatives which have aromatic substitution in the amino
position. They are said to have high α -adrenoceptor
affinity and to be useful as antihypertensives. An
abstract of the latter reference (CA 114:42158) depicts as
30 an example of a compound included within the scope of this
disclosure the structure 2-(2,6-dimethylphenoxy)-1-
methylethyl]-n-propylamine. However, an English
translation of this article does not appear to disclose
such a derivative.

35

U.S. Patent No. 2,441,498 (Löfgren et al.) discloses lidocaine, 2-(diethylamino)-N-(2,6-dimethylphenyl)acetamide, and its use as a local anesthetic and antiarrhythmic. U.S. Patent Nos. 3,221,054 (Köppe et al.) discloses 1-(2,6-dimethylphenoxy)-2-methylaminopropane (alternatively named as [2-(2,6-dimethylphenoxy)-1-methylethyl]methylamine) as useful as an intermediate in the synthesis of monoamine oxidase inhibitors, and 4,105,796 (Arnold et al.) discloses the same compound as useful for suppressing convulsions or alleviating cardiac arrhythmia. U.S. Patent No. 2,895,995 (Lawrence et al.) discloses the preparation of local anesthetics β -(2,6-xylyloxy)ethyldimethylamine and β -(2,6-xylyloxy)-ethyldiethylamine and their quaternary ammonium salts. However, the use of lidocaine is limited by its potential for cardiotoxic and CNS side effects.

Published Great Britain Patent Application No. 1,112,839 discloses 1-(p-chloro)-2-ethylaminopropane, 1-(m-chloro)-2-ethylaminopropane, and 1-(2,3-dichloro)-2-ethylaminopropane compounds possessing anorexigenic activity, their preparation, and compositions. U.S. Patent Nos. 3,475,455 and 3,515,741 disclose 1-(2'-cyanophenoxy-2-ethylamino)propane, 1-(3'-cyanophenoxy-2-ethylamino)propane, 1-(4'-cyanophenoxy-2-ethylamino)propane, their salts, preparation, and compositions. Published Belgium Patent Application No. 691,209 discloses racemic or optically active 1-(4'-nitrilo)-phenoxy-2-ethylaminopropane and 1-(3',4'-methylenedioxy)-phenoxy-2-ethylaminopropane, their preparation and compositions.

The disclosures of these and other documents referred to throughout this application are incorporated herein by reference.

It can therefore be seen that a need still exists for an orally active agent that is effective for the treatment of neuropathic pain, but having low side effects. Surprisingly, we have discovered a compound with this
5 desired spectrum of activity, namely [2-(2,6-dimethylphenoxy)-1-methylethyl]ethylamine, and in particular its (*R*)- enantiomer.

The compound of Formula I is unexpectedly more active
10 in standard assays when compared with close analogues, for example [2-(2,6-dimethylphenoxy)-1-methylethyl]methylamine and [2-(2,6-dimethylphenoxy)-1-methylethyl]-*n*-propylamine and isomers thereof.

15 In addition, for drugs that are racemic mixtures it is well known that the therapeutic activity usually resides in one of the enantiomers. The other enantiomer may be pharmacologically inactive, or have different therapeutic activities. Surprisingly, the (*R*)- and the (*S*)-enantiomers
20 of [2-(2,6-dimethylphenoxy)-1-methylethyl]ethylamine both display similar activity in neuropathic pain models, but deleterious side effects are largely confined to the (*S*)-enantiomer.

25 A second aspect of this invention relates to pharmaceutical compositions containing the compound of Formula I, in admixture with one or more suitable excipients.

30 A third aspect of this invention relates to use of the compound of Formula I for treating neuropathic pain conditions in a mammal that is responsive to sodium channel-blocking agents, including:

peripheral neuropathies, such as trigeminal neuralgia, -
posttherapeutic neuralgia, diabetic neuropathy,
glossopharyngeal neuralgia, radiculopathy, and neuropathy
secondary to metastatic infiltration, adiposis dolorosa,
5 and burn pain; and

central pain conditions following stroke, thalamic
lesions and multiple sclerosis, by administering a
therapeutically effective amount of a compound of Formula
I to the mammal.

10

It should be understood that Formula I as drawn is
intended to represent the racemic form of Formula I as
well as the individual enantiomers and non-racemic
mixtures thereof. The racemic form is named as [2-(2,6-
15 dimethylphenoxy)-1-methylethyl]ethylamine, and the two
enantiomers are (R)-[2-(2,6-dimethylphenoxy)-1-
methylethyl]ethylamine and (S)-[2-(2,6-dimethylphenoxy)-1-
methylethyl]ethylamine. The individual enantiomers may be
obtained by resolving a racemic or non-racemic mixture of
20 an intermediate at some appropriate stage of the
synthesis, or by resolution of a compound of Formula I. It
is understood that the individual enantiomers as well as
racemic and non-racemic mixtures of enantiomers are
encompassed within the scope of the present invention.
25 When the compound of Formula I is a pure enantiomer, the
stereochemistry is specified by either R or S according to
the Cahn-Ingold-Prelog R-S system. In this manner relative
stereochemistry is conveyed unambiguously.

30

"Isomers" are different compounds that have the same
molecular formula.

"Stereoisomers" are isomers that differ only in the
way the atoms are arranged in space.

35

"Enantiomers" are a pair of stereoisomers that are non-superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a "racemic" mixture.

5 "Mammal" includes humans and all domestic and wild mammals, including without limitation, cattle, horses, swine, sheep, goats, dogs, cats, rabbits and the like.

10 "Pharmaceutically acceptable" refers to that which is useful in preparing a pharmaceutically composition that is generally safe, non-toxic, and neither biologically nor otherwise undesirable, and includes that which is acceptable for veterinary use as well as human pharmaceutical use.

15 "Pharmaceutically acceptable salts" refers to those salts which are pharmaceutically acceptable, as defined above, and which possess and retain the desired pharmacological activity of the compound of Formula (I).
20 The compound of Formula (I) form acid addition salts by virtue of the presence of the basic nitrogen atom. Acid addition salts may be formed with inorganic salts such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids
25 such as acetic acid, propionic acid, hexanoic acid, heptanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, o-(4-hydroxybenzoyl)- benzoic
30 acid, cinnamic acid, mandelic acid, methanesulfonic acid, p-toluenesulfonic acid, camphorsulfonic acid, 4-methyl-bicyclo[2.2.2.]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary
35 butylacetic acid, lauryl sulfuric acid, gluconic acid,

glutamic acid, hydroxynaphthoic acid, salicyclic acid, -
stearic acid, muconic acid, tartaric acid and the like.

Preferred pharmaceutically acceptable salts of [2-(2,6-
dimethylphenoxy)-1-methylethyl]ethylamine are acid

5 addition salts formed from inorganic acids. A particularly
preferred pharmaceutically acceptable salt is [2-(2,6-
dimethylphenoxy)-1-methylethyl]ethylamine hydrochloride.

"Treatment" as used herein covers any treatment of a
10 condition in a mammal, particularly a human, and includes:

(i) preventing the disease from occurring in a subject
which may be predisposed to the disease, but has not yet
been diagnosed as having it;

15 (ii) inhibiting the condition, i.e., arresting its
development; or

(iii) relieving the condition, i.e., causing
regression of the disease.

20 The term "disease state which is alleviated by
treatment with a sodium channel blocker" as used herein is
intended to cover all disease states which are generally
acknowledged in the art to be usefully treated with sodium
channel blockers in general, and those disease states
25 which have been found to be usefully treated by the
specific sodium channel blocker of our invention, the
compound of Formula I. Such disease states include, but
are not limited to, arrhythmia, pain associated with
damage or permanent alteration of the peripheral or
30 central nervous system, for example peripheral
neuropathies, such as trigeminal neuralgia, posttherapeutic
neuralgia, diabetic neuropathy, glossopharyngeal
neuralgia, and neuropathy secondary to metastatic
infiltration, adiposis dolorosa, and burn pain; and
35 central pain conditions following stroke, thalamic lesions

and multiple sclerosis.

5 The term "therapeutically effective amount" refers to that amount which is sufficient to effect treatment, as defined above, when administered to a mammal in need of such treatment. The therapeutically effective amount will vary depending on the subject and disease state being treated, the severity of the affliction and the manner of administration, and may be determined routinely by one of
10 ordinary skill in the art.

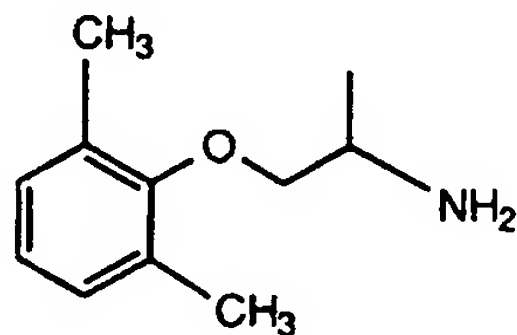
"Analgesia" is an absence of pain in response to a stimulus that would normally be painful.

15 "Allodynia" refers to a condition in which ordinary stimulation, such as pressure or light touch, is perceived as being extremely painful.

"E_{max}" refers to the maximal effect of a drug in a
20 particular assay.

"ED₅₀" identifies the dose of a drug that elicits 50% of the maximal effect.

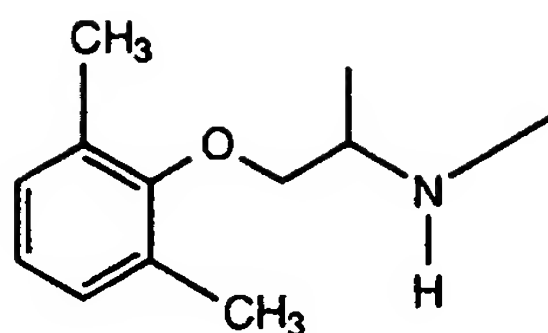
25 1-(2,6-Dimethylphenoxy)-2-propanamine, also known as mexiletine, is identified herein as a compound of Formula II:



II

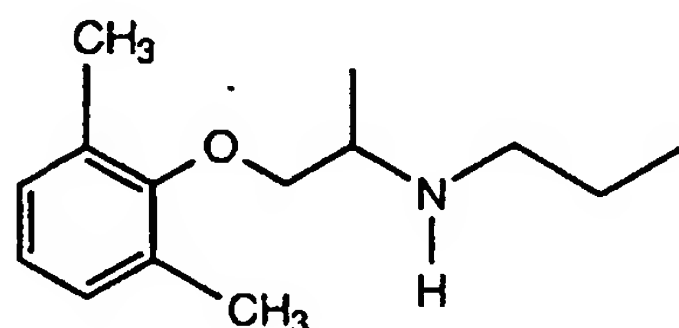
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[2-(2,6-Dimethylphenoxy)-1-methylethyl]methylamine is identified herein as a compound of Formula III:



III

5 2-(2,6-Dimethylphenoxy)-1-methylethyl]-n-propylamine
is identified herein as a compound of Formula IV:



IV

Utility

10 The compound of Formula I and its pharmaceutically
acceptable acid addition salts thereof have been found to
possess valuable pharmacological properties. In
particular, they have been shown to be useful as sodium
channel blockers in standard laboratory tests. Accordingly
15 this compound and pharmaceutically acceptable compositions
containing them are useful in the regulation of
physiological phenomena related to sodium channel
blockade, including arrhythmia, convulsion, pain
associated with damage or permanent alteration of the
20 peripheral or central nervous system, for example
peripheral neuropathies, such as trigeminal neuralgia,
postherapeutic neuralgia, diabetic neuropathy,
glossopharyngeal neuralgia, and neuropathy secondary to
metastatic infiltration, adiposis dolorosa, and burn pain;
25 and central pain conditions following stroke, thalamic
lesions and multiple sclerosis.

Testing

Interaction with ligand binding sites on voltage-gated sodium channels is determined in radioligand binding assays, described in Example 10.

5

Potential for sodium channel blocking activity is determined *in vitro* by the method of Kourtney and Stricharz (1987), Local Anesthetics, Springer-Verlag, New York, described in Example 11.

10

The mechanical allodynia activity is determined *in vivo*, described in Example 12.

15

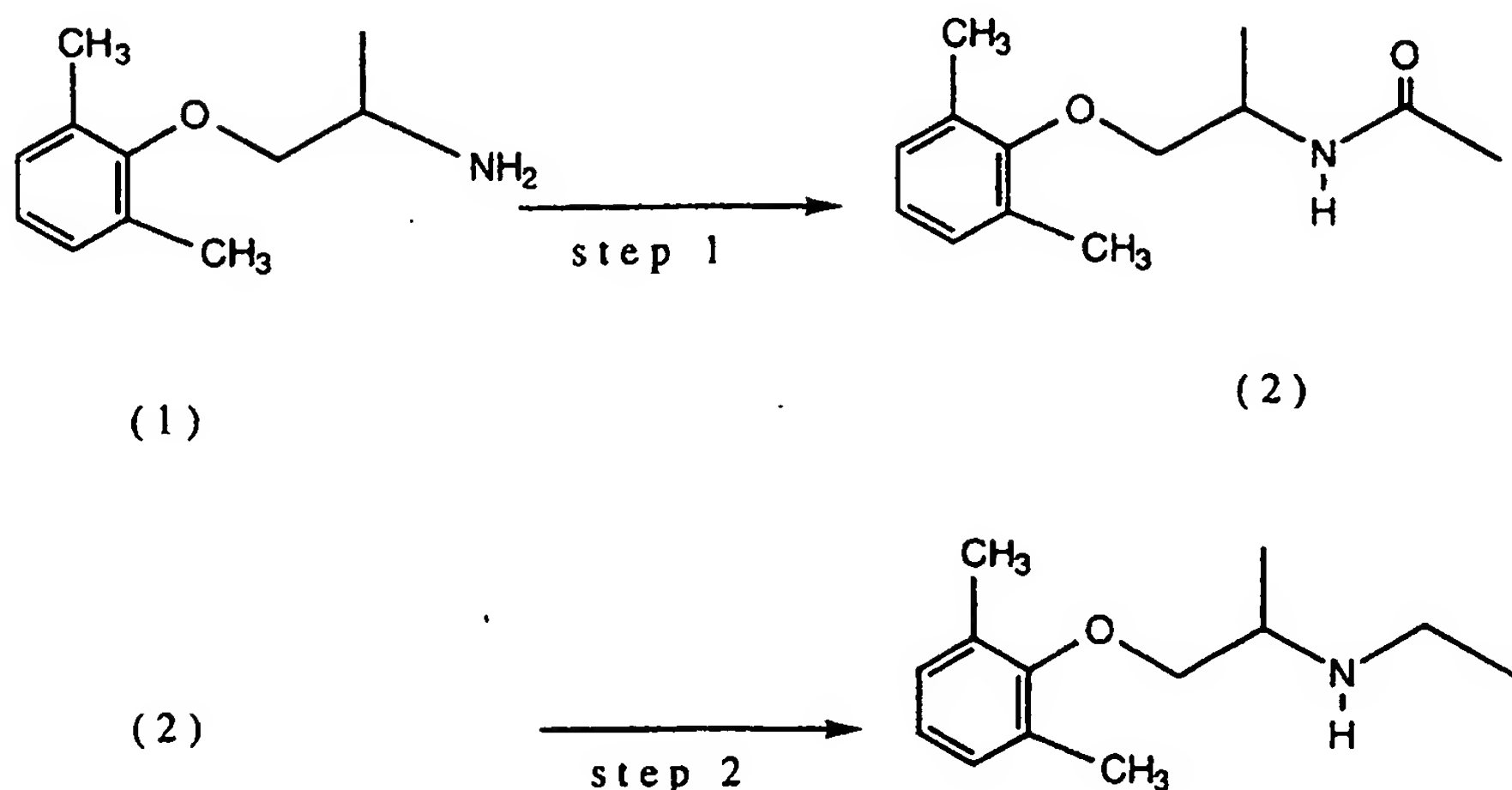
The cold allodynia activity is determined *in vivo*, described in Example 13.

Preparation of Compound of Formula I:

20

The racemic compound of Formula I is prepared from the intermediate of Formula (2), as shown below in Reaction Scheme I.

REACTION SCHEME I



5 In Step 1, 1-(2,6-dimethylphenoxy)-2-propanamine
 (mexiletine) is converted to mexiletine acetamide.
 Mexiletine is treated with an acetylating agent, such as
 an acetyl chloride or acetic anhydride, in the presence of
 concentrated aqueous alkali and an organic solvent, e.g.,
 10 ethyl acetate. The reaction temperature is maintained at
 about 0°-25°C, preferably below 10°C, for about 10 minutes
 to 3 hours, preferably about 35 minutes. Following
 completion of the reaction, the resulting *N*-[2-(2,6-
 dimethylphenoxy)-1-methylethyl]acetamide is isolated by
 15 conventional techniques, and used as such in Step 2.

It should be noted that replacing racemic mexiletine
 with one of its enantiomers and carrying out the above
 reactions gives *N*-[2-(2,6-dimethylphenoxy)-1-
 20 methylethyl]acetamide in optically active form.

Step 2 involves the reduction of the *N*-[2-(2,6-
 dimethylphenoxy)-1-methylethyl]acetamide to the amine. The
 product from step 1 is heated to reflux temperature in the

presence of an aprotic solvent such as tetrahydrofuran,
and an effective reducing agent such as borane-disulfide
complex. The reaction temperature is maintained at reflux
for about 5-40 hours, preferably about 24 hours, and is
5 preferably performed under an inert atmosphere, e.g.,
nitrogen. When the reaction is substantially complete, the
product is isolated and purified by conventional
techniques, for example converting to an acid salt,
preferably the hydrochloride salt, then crystallizing from
10 an organic solvent, for example ethanol/ether, yielding
racemic [2-(2,6-dimethylphenoxy)-1-methylethyl]ethylamine
salt, preferably the hydrochloride salt.

It should be noted that replacing the racemic compound
15 of Formula (2) with *N*-[2-(2,6-dimethylphenoxy)-1-
methylethyl]acetamide in optically active form gives the
compound of Formula I in optically active form.

Similarly, two analogues of the compound of Formula I
20 compounds were prepared for comparison purposes, namely
[2-(2,6-dimethylphenoxy)-1-methylethyl]methylamine and [2-
(2,6-dimethylphenoxy)-1-methylethyl]-*n*-propylamine of
formulae III and IV above. The methylamine analogue III is
prepared by first reacting the compound of Formula (1) by
25 methods well known in the art, for example with ethyl
chloroformate, and then reducing the *N*-formyl compound
thus produced with lithium aluminum hydride. The *n*-
propylamine analogue IV was prepared in the same manner as
shown above for a compound of Formula I, replacing acetyl
30 chloride by propionyl chloride.

The compound of Formula I may be resolved into its
enantiomers by conventional resolution means, for example,
by separation (e.g., fractional crystallization) of the
35 diastereomeric salts formed by the reaction of a compound

of Formula I (as its free base) with an optically active —
acid, at temperatures between 0°C and the reflux
temperature of the solvent employed for fractional
crystallization, for example isopropanol. Exemplary of
5 such optically active acids are the optically active forms
of camphor-10-sulfonic acid, 2-bromo-camphor-10-sulfonic
acid, camphoric acid, menthoxyacetic acid, tartaric acid,
malic acid, diacetyltartaric acid,
pyrrolidine-5-carboxylic acid, and the like, preferably
10 tartaric acid. The separated pure diastereomeric salts may
then be cleaved by standard means, such as treatment with
a base, to afford both enantiomers of the compound of
Formula I.

15 For example, resolution with D-tartaric acid gives the
(R)-enantiomer of the compound of Formula I; starting with
L-tartaric acid gives the (S)-enantiomer.

Alternatively, the (R)- and (S)- enantiomers of the
20 compound of Formula I are prepared as described above.
i.e., acetylation of optically pure mexiletine, followed
by reduction of the acetamide thus produced.

The invention is illustrated without limitation by the
25 following Examples.

Example 1

Preparation of a Compound of Formula (2)

30 1A. Acetyl chloride (99 ml, 1.39 mol, 1.5 eq) was added to
a stirred suspension of mexiletine hydrochloride (200 g,
0.927 mol), ethyl acetate (750 ml), and 5N sodium
hydroxide (750 ml) over a period of 35 minutes while
keeping the temperature at $\leq 10^\circ\text{C}$. After the addition was
35 complete, the reaction was allowed to stir for 45 minutes

at 15-20°C. The mixture was then added to water (1 l) and the ethyl acetate layer separated. The aqueous layer was washed with ethyl acetate (2x300 ml) and the combined ethyl acetate layers were washed with saturated aqueous sodium bicarbonate until the washings were no longer acidic. The ethyl acetate solution was then washed with brine, dried over MgSO₄, and concentrated to give N-[2-(2,6-dimethylphenoxy)-1-methylethyl]acetamide (197 g, 96% yield, mp 85-85.8°C).

10

1B. Similarly, replacing acetyl chloride with ethyl chloroformate, [2-(2,6-dimethylphenoxy)-1-methylethyl]-formamide was made.

15

Similarly, replacing acetyl chloride with propionyl chloride, [2-(2,6-dimethylphenoxy)-1-methylethyl]-n-propionamide was made.

Example 2

20

Preparation of a Compound of Formula I

2A. Borane-dimethylsulfide complex (10-10.2M, 35 ml, 1.2 eq) was added to a refluxing solution of N-[2-(2,6-dimethylphenoxy)-1-methylethyl]acetamide (68 g, 0.289 mol) and tetrahydrofuran (400 ml) under a nitrogen atmosphere. After the addition was complete, the reaction was allowed to reflux for 25 hours. The reaction was then cooled to room temperature and 10% hydrochloric acid/ethanol was added until the mixture was acidic. After concentration of the reaction mixture, ethyl ether was added to induce crystallization. The solids were isolated by filtration and dried to give N-[2-(2,6-dimethylphenoxy)-1-methylethyl]ethylamine hydrochloride salt (53.0 g, 75% yield, mp 184.7-185.8°C).

35

2B. Similarly, replacing N-[2-(2,6-dimethylphenoxy)-1-methylethyl]-acetamide with [2-(2,6-dimethylphenoxy)-1-methylethyl]formamide, and replacing borane-dimethyl-sulfide complex with lithium aluminum hydride, [2-(2,6-dimethylphenoxy)-1-methylethyl]methylaniline was made.

Similarly, replacing N-[2-(2,6-dimethylphenoxy)-1-methylethyl]acetamide with [2-(2,6-dimethylphenoxy)-1-methylethyl]-n-propionamide, [2-(2,6-dimethylphenoxy)-1-methylethyl] n-propylaniline was made.

Example 3

Preparation of the Enantiomers of the Compound of Formula I

3A. An aqueous solution of racemic N-[2-(2,6-dimethylphenoxy)-1-methylethyl]ethylaniline hydrochloride (41.1 g, 0.169 mol) was made alkaline with potassium hydroxide and extracted with ethyl acetate (3x250 ml). The combined ethyl acetate layers were washed with brine, dried over MgSO_4 , and concentrated to give the free base (36 g). The free base was dissolved in isopropanol (750 ml), and D-tartaric acid (25.3 g, 0.168 mol) was added. The resultant solid was filtered, dried, and recrystallized to give (1R,2'S,3'S)-(-)-2-(2,6-dimethylphenoxy)-1-methylethyl-ethylaniline tartrate salt (18.5 g, mp 161.4-162.7°C, $[\alpha]_D = -19.0^\circ$, 97% ee as determined by chiral HPLC analysis).

An aqueous solution of the tartrate salt (18.0 g) was made alkaline with aqueous potassium hydroxide and washed with ethyl acetate (4x250 ml). The combined ethyl acetate layers were washed with brine, dried over MgSO_4 , and concentrated to give an oil. This oil was dissolved in ethyl ether (500 ml) and made acidic with anhydrous

hydrochloric acid in ether. The precipitated solids were isolated by filtration and recrystallized from ethyl alcohol to give (R)-(-)-2-(2,6-dimethylphenoxy)-1-methylethyl)ethylamine hydrochloride salt (8.3 g, 75% yield, mp 187-187.4°C, $[\alpha]_D = -11.8^\circ$).

3B. Similarly, replacing D-tartaric acid with L-tartaric acid and following the procedure of 3A above, (S)-(-)-2-(2,6-dimethylphenoxy)-1-methylethyl)ethylamine hydrochloride was prepared.

Example 4

This example illustrates the preparation of a representative pharmaceutical formulation for oral administration containing an active compound of Formula I, e.g., (R)-(-)-2-(2,6-dimethylphenoxy)-1-methylethyl)-ethylamine hydrochloride.

20	<u>Ingredients</u>	<u>Quantity per tablet, mgs.</u>
	Active Compound	200
	Lactose, spray-dried	148
	Magnesium stearate	2

25

The above ingredients are mixed and introduced into a hard-shell gelatin capsule.

Other compounds of Formula I can be used as the active compound in the preparation of the orally administrable formulations of this example.

30

Example 5

5 This example illustrates the preparation of another representative pharmaceutical formulation for oral administration containing an active compound of Formula I, e.g., (R)-(-)-2-(2,6-dimethylphenoxy)-1-methylethyl)-ethylamine hydrochloride.

	<u>Ingredients</u>	<u>Quantity per tablet, mgs.</u>
10	Active Compound	400
	Cornstarch	50
	Lactose	145
	Magnesium stearate	5

15

The above ingredients are mixed intimately and pressed into single scored tablets.

20 Other compounds of Formula I can be used as the active compound in the preparation of the orally administrable formulations of this example.

Example 6

25 This example illustrates the preparation of a representative pharmaceutical formulation containing an active compound of Formula I, e.g., (R)-(-)-2-(2,6-dimethylphenoxy)-1-methylethyl)ethylamine hydrochloride.

30 An oral suspension is prepared having the following composition.

Ingredients

	Active Compound	1.0	g
	Fumaric acid	0.5	g
5	Sodium chloride	2.0	g
	Methyl paraben	0.1	g
	Granulated sugar	25.5	g
	Sorbitol (70% solution)	12.85	g
	Veegum K (Vanderbilt Co.)	1.0	g
10	Flavoring	0.035	ml
	Colorings	0.5	mg
	Distilled water	q.s. to 100	
	ml		

15 Other compounds of Formula I can be used as the active compound in the preparation of the orally administrable formulations of this example.

Example 7

20

This example illustrates the preparation of a representative pharmaceutical formulation for oral administration containing an active compound of Formula I, e.g., (R)-(-)-2-(2,6-dimethylphenoxy)-1-methylethyl)-ethylamine hydrochloride.

25

An injectable preparation buffered to a pH of 4 is prepared having the following composition:

30

Ingredients

	Active Compound	0.2	g
	Sodium Acetate Buffer Solution (0.4 M)	2.0	ml
	HCL (1N)	q.s. to pH 4	
35	Water (distilled, sterile)	q.s. to 20 ml	

Other compounds of Formula I can be used as the active compound in the preparation of the injectable formulations of this example.

5

Example 8

This example illustrates the preparation of a representative pharmaceutical formulation for topical application containing an active compound of Formula I, e.g., (R)-(-)-2-(2,6-dimethylphenoxy)-1-methylethyl)-ethylamine hydrochloride.

10

15

Ingredients	grams
Active compound	0.2-10
Span 60	2
Tween 60	2
Mineral oil	5
20 Petrolatum	10
Methyl paraben	0.15
Propyl paraben	0.05
BHA (butylated hydroxy anisole)	0.01
Water	q.s. to 100

25

30

All of the above ingredients, except water, are combined and heated to 60°C with stirring. A sufficient quantity of water at 60°C is then added with vigorous stirring to emulsify the ingredients, and water then added q.s. 100 g.

35

Other compounds of Formula I can be used as the active compound in the preparation of the topical formulations of this example.

- 20 -

Example 9

5 This example illustrates the preparation of a representative pharmaceutical formulation containing an active compound of Formula I, e.g., (R)-(-)-2-(2,6-dimethylphenoxy)-1-methylethyl)ethylamine hydrochloride.

10 A suppository totalling 2.5 grams is prepared having the following composition:

Ingredients

Active Compound	500 mg
Witepsol H-15*	balance

15 (*triglycerides of saturated vegetable fatty acid; a product of Riches-Nelson, Inc., New York, N.Y.)

20 Other compounds of Formula I can be used as the active compound in the preparation of the suppository formulations of this example.

Example 10

Radioligand Binding Assays

25 The following assays characterize the interaction of the compounds of Formula I with ligand binding sites on voltage-gated sodium channels.

30 10A. Preparation of cell membranes

Frozen tissues were obtained from Pel-Freez Biologicals (Rogers, AR). Tissues were homogenized in 10 volumes of a Tris-sucrose buffer (10 mM Tris-HCl, 250 mM sucrose, pH 7.4 at 4°C) using 10 strokes with a glass-glass, hand-held homogenizer. The homogenates were

35

filtered through nylon mesh and then centrifuged at 1,000 x g for 15 minutes. The pellets were resuspended in a Hepes buffer (50 mM Hepes, 130 mM choline chloride, 5 mM glucose, 5.4 mM KCl, pH 7.4 at 4°C). The resuspended
5 pellets were centrifuged at 1,000 x g for 15 minutes, resuspended in a Hepes buffer (50 mM Hepes, 130 mM choline chloride, 5 mM glucose, 5.4 mM KCl, pH 7.4 at 25°C) and, frozen at -70°C until used in binding assays.

10 10B. [³H]BTX Binding Assay

Cell membranes prepared as in Example 10A above were incubated with 16 nM [³H]BTX in 250 µl of Hepes buffer (50 mM Hepes, 130 mM choline chloride, 5 mM glucose, 5.4 mM KCl, pH 7.4 at 25°C). Nonspecific binding was defined in
15 the presence of 1 mM veratridine. Unless otherwise specified, PbTx (0.1 µM) and LqTx (50 µg/ml) were included in the assays. Membranes were incubated for 60 minutes at 25°C and then filtered using GF/B glass fiber filters that had been pretreated with 0.3% PEI. Filters were rinsed
20 with 3 x 1 ml of ice cold 50 mM Tris-HCl (pH 7.4 at 4°C) and the bound radioactivity was determined by scintillation counting (Packard Top-count).

The racemate of Formula I inhibited [³H]BTX binding in
25 rat cortex, rat heart, and rat dorsal root ganglion tissue membranes. The potency of the racemate was found to be approximately 10 fold greater in the rat cortex than in rat heart or rat dorsal root ganglion. Similar potencies were obtained with mexiletine. There was no difference in
30 the potencies of the (R)- or (S)-enantiomers of Formula I in inhibiting [³H]BTX binding to rat brain cortex membranes. This indicates that the racemate and the (R)- and (S)-enantiomers are sodium channel ligands which inhibit channel function by binding on the local
35 anesthetic site on the channel.

10C. [³H]STX Binding Assay

Membranes as prepared in Example 10A above were incubated at 37°C for 30 minutes in 250 µl of a Hepes buffer (50 mM Hepes, 130 mM choline chloride, 5.5 mM glucose, 0.8 mM MgSO₄, 5.4 mM KCl, pH 7.4 at 37°C) containing 1 nM [³H]STX. Nonspecific binding was defined with 1 µM tetrodotoxin (TTX). Reactions were terminated by filtration through GF/B glass fiber filters pretreated with 0.1% PEI. The filters were rinsed with 3 x 1 ml ice cold H₂O and the bound radioactivity determined in a Packard 1900 liquid scintillation counter using Aquasol scintillation fluid.

The racemate of Formula I exhibited no detectable affinity for the [³H]STX binding site on the rat brain sodium channel.

10D. [³H]PD85639 Binding Assay

Membranes as prepared in Example 10A above were incubated with 3 nM [³H]PD85639 in 250 µl of Hepes buffer (50 mM Hepes, 130 mM choline chloride, 5 mM glucose, 5.4 mM KCl, pH 7.4 at 25°C with Tris base). Nonspecific binding was defined in the presence of 0.1 mM PD85639. Membranes were incubated for 60 minutes at 25°C and then filtered using GF/B glass fiber filters that had been pretreated with 0.3% PEI. Filters were rinsed with 3 x 1 ml of ice cold 50 mM Tris-HCl (pH 7.4 at 4°C) and the bound radioactivity was determined by scintillation counting (Packard Top-count).

The racemate of Formula I inhibited [³H]PD85639 to the local anesthetic site of the sodium channel in rat brain cortex membranes. Mexiletine exhibited similar affinity estimates.

10E. [¹⁴C]Guanidinium Ion Influx Binding Assay

Chinese hamster ovary cells stably expressing the rat brain type IIA sodium channel subunit were maintained in RPMI 1640 with 10% fetal bovine serum and 300 µl/ml G-418. Chinese hamster lung cells stably expressing the human heart (hH1a) sodium channel subunit were maintained in DMEM with 5% fetal bovine serum and 300 µg/ml G-418. Both cells were subcultured and grown to confluence in 24-well plates 2-3 days before each experiment. After the growth medium was removed, the cells were washed with warm buffer (25 mM Hepes-Tris, 135 mM choline chloride, 5.4 mM potassium chloride, 0.98 mM magnesium sulfate, 5.5 mM glucose, and 1 mg/ml BSA, pH 7.4) and incubated in buffer on a 36°C slide warmer for approximately 10 minutes. Various concentrations of the test compounds or standard sodium channel blockers (10 µl) and then veratridine (100 µM) were added to each well. After the cells were exposed to veratridine for 5 minutes, 5 µM of [¹⁴C]guanidinium was added, incubated with the radioligand, washed with 4 ml of ice-cold buffer, and dissolved in 0.1N sodium hydroxide. The radioactivity and the protein concentration of each cell lysate were determined by liquid scintillation counting and the protein assay using Pierce BCA reagent.

25

The racemate of Formula I inhibited veratridine-stimulated [¹⁴C]Guanidinium ion influx through both rat brain and human heart sodium channels with the similar potencies being exhibited through rat brain and human heart sodium channels.

30

Example 11Test for Blockade of Sodium Channels - *in Vitro* Assay

35

This assay demonstrates the ability of the compounds

of Formula I to function as sodium channel blockers, by producing a blockade of high frequency nerve activity in the rat vagus nerve.

5 Vagus nerves were removed from rats, continually
superfusing them with control solutions or solutions of
the compounds under test. Electric shocks were applied to
the nerve to stimulate the propagation of nerve impulses.
The amplitude of the synchronous compound action potential
10 was measured; it was reduced as the sodium channels became
blocked by the perfused compounds.

 There is good agreement between the sodium channel
blocking potency as determined by this assay and those
15 measured by other methods, for example the voltage-
clamping technique. The compounds of our invention showed
activity as sodium channel blockers in this test.

Example 12

20 Mechanical Allodynia In Vivo Assay

 This assay determines the effectiveness of compounds
in relieving one of the symptoms of neuropathic pain
produced by spinal nerve ligation, namely mechanical
25 allodynia.

12A. The Surgery

 The surgical procedure was performed essentially as
described by Kim and Chung, *Pain*, (1992) 50:355-363.
30 Briefly, the rats were anesthetized with an
intraperitoneal dose of pentobarbital sodium (65 mg/kg)
with additional doses of anesthetic given as needed. Each
animal was then placed in a prone position, a 3 cm lateral
incision was made, and the left paraspinal muscles
35 separated from the spinous process at the L₄-S₂ level. The

L₆ transverse process was then removed in order to visually identify the L₄-L₆ spinal nerves. The L₅ and L₆ spinal nerves were then individually isolated and tightly ligated with silk thread. The wound was then closed in layers by silk sutures.

12B. The Mechanical Allodynia Assay

Seven to 28 days post-surgery, a calibrated series of eight von Frey filaments were used to assess mechanical allodynia. Animals were housed individually in plexiglass cages with a wire mesh floor. Filaments of increasing stiffness were applied perpendicular to the midplantar surface in the sciatic nerve distribution areas of the left hindpaw and were slowly depressed (4-6 seconds) until bending occurred. The filament application order and number of trials were determined by the up-down paw method of Dixon (Chaplan, et al., *J. Neurosci. Methods*, (1994) 53:55-63). Flinching and licking of the paw and paw withdrawal on the ligated side were all considered positive responses. The 50% paw withdrawal threshold (g) was then calculated and compared to control.

12C. The Selection of Doses

The doses for the acute and chronic studies were selected on the basis of prior assessment of the acute effects on the test compounds on the gross behavior in normal rats. Briefly, three groups of rats were weighed and grouped into cages, dosed with the test compound, and observed continuously for changes in behavior. At 60 and 120 minutes post-dose, the rats were observed for pinna, corneal and righting reflexes. Pinna and corneal reflexes were tested by using a piece of natural hair from a brush that is attached to a glass rod. The righting reflexes were tested by placing the rat flat on its back, and recording the time it takes for the animal to right itself

onto all four legs. The posture and gait were assessed by placing the rat on the floor.

12D. The Results of Subcutaneous Administration

5

Compound Formula	Chiral form	Dose (mg/kg)	ED ₅₀	E _{max}
I	racemate	3-60	12.6	66%
II	racemate	30-100	no value at these doses	29%
III	racemate	10-100	31.3	67%
IV	racemate	10-30	not tested due to adverse events at higher doses	

The results show that after subcutaneous administration, the compound of Formula I was considerably more potent (ED₅₀) than II or III in the mechanical allodynia test. Compound IV was less potent than compound III at the 30 mg/kg single dose level, and further escalation of the dose-range was prevented by the onset of adverse events, including convulsions and severe ataxia at 60 mg/kg.

15

In contrast, when tested in this assay the (R)-enantiomer of Formula I exhibited significantly greater maximal analgesic activity (98% E_{max}) in vivo against mechanical allodynia than either the racemate of I (66% E_{max}), the racemate of II (29% E_{max}), and the racemate of III (67% E_{max}).

20

12E. The Results of Oral Administration

The results show that after oral administration, the (R)- or (S)-enantiomers of Formula I or the racemate of Formula II did not produce analgesia against mechanical allodynia. However, the (S)-enantiomer of I was associated with adverse side effects at doses greater than 60 mg/kg,

25

whereas the (R)-enantiomer of I exhibited a cleaner safety profile with adverse effects occurring only at doses \geq 300 mg/kg.

5

Example 13

Cold Allodynia In Vivo Assay

This assay determines the effectiveness of compounds in relieving one of the symptoms of neuropathic pain produced by unilateral mononeuropathy, namely cold allodynia.

13A. The Surgery

Unilateral mononeuropathy was produced in rats using the Chronic Constriction Injury model performed essentially as described by Bennet and Xie, Pain, (1988) 33:87-107. Briefly, the rats were anesthetized with an intraperitoneal dose of pentobarbital sodium (65 mg/kg) with additional doses of anesthetic given as needed. The lateral aspect of each rat's hind limb was shaved and scrubbed with Novasan. Using aseptic technique, an incision was made on the lateral aspect of the hind limb at the mid-thigh level. The biceps femoris was bluntly dissected to expose the sciatic nerve. On the right hind limb of each rat, four loosely tied ligatures were made around the sciatic nerve approximately 1-2 millimeters apart. On the left side of each rat, an identical dissection was performed except that the sciatic nerve was not ligated. The muscle and skin were closed with a continuous suture pattern.

13B. The Cold Allodynia Assay

Each rat was placed individually into a plexiglass chamber which with a metal plate 6 cm from the bottom. This chamber was filled with ice water to a depth of 2.5

cm above the metal place, with the temperature of the bath maintained at 0°C throughout the experiment. A timer was started, and the rat's response latency was measured to the nearest tenth of a second. A "response" was defined as a rapid withdrawal of the right ligated hindpaw completely out of the water while the animal was stationary and not pivoting. An exaggerated limp while the animal was walking was not scored as a response. Maximum immersion time was 20 seconds with a 20 minute interval between trials. The screening criteria were 1) the average of two trials was less than or equal to 13 seconds, and 2) there was consistency across the two trial scores. Animals were screened for hypersensitivity to cold on post-surgery days 4 through 10, and selected for inclusion in dose-response studies based on the criteria described above. The pre-dose screening values were used as the animal's baseline cold allodynia scores.

13C. The Experimental Design

For acute studies, the animals received either subcutaneous or oral injections and were tested for cold allodynia at 1, 3, and sometimes 5 hours post-dose.

For chronic studies, the animals received subcutaneous or oral injections twice daily for 4 days and once on day 5. The animals were tested for allodynia on day 1 at 1, 3 and 5 hours following the 8 am dose, and at 5 hours following the 8 am dose on days 3 and 5. Two days later, the animals were tested for cold allodynia to assess whether there was a wash-out of the drug being tested. Following this screening for cold allodynia, the animals in two of the three chronic studies received either subcutaneous or oral injections of the drug at a dose previously shown to produce significant anti-allodynic effects acutely. One hour after this dosing, the animals

were again tested for cold allodynia.

13D. The Selection of Doses

The selection of doses was similar to that of Example 12C.

13E. The Results of Subcutaneous Administration - Acute Studies

Compound	Chiral Form	Dose mg/kg	ED ₅₀		E _{max}	
			1 hr	3 hr	1 hr	3 hr
I	racemate	10-60	15.7	N/D	82%	N/D
I	(S)-	10-60	12.8	10.0	100%	58%
I	(R)-	10-100	37.0	23.4	91%	87%
II	racemate	10-100	29.8	33.6	73%	80%
III	(R)-	10-100	26.1	31.4	76%	74%
IV	(R)-	10-60	28.4	29.9	74%	74%

N/D = not able to determine.

Example 13E shows the results for the acute studies following subcutaneous administration. The compounds of Formula I, III and IV when tested as the (R)-isomer exhibited comparable potency (ED₅₀), but compound I as the (R)-isomer exhibited significantly greater maximal analgesic activity (E_{max}) than III or IV in the inhibition of cold allodynia. It should be noted that the racemate and the (S)-enantiomer of Formula I were associated with adverse side effects, including convulsions and immobility, at doses higher than 60 mg/kg; the (R)-enantiomer of Formula IV produced behavioral problems, including splayed limbs and abnormal righting reflexes, at doses higher than 60 mg/kg. The (R)-enantiomer of Formula

I, on the other hand, suggested a greater maximal analgesic activity, a cleaner safety profile with adverse side effects not observed until doses of 300 mg/kg were used, and a longer duration of action in vivo over the racemate, (S)-enantiomer, or II.

13F. The Results of Subcutaneous Administration - Chronic Studies

For the chronic studies administered subcutaneously, the doses of compound I that were inactive in the acute studies (5 mg/kg for the racemate; 10 and 20 mg/kg for the (R)-isomer) produced no significant anti-allodynic effects when tested at 1, 3 or 5 hours post-dose; however, after 5 days of twice daily dosing, the racemate and (R)-isomer produced significant levels of anti-allodynia. The same study when repeated for compound II showed no significant anti-allodynic effects for chronic administration.

13G. The Results of Oral Administration - Chronic Studies

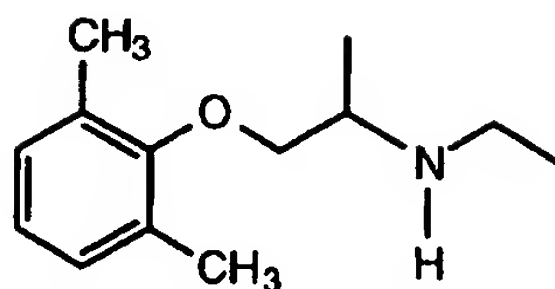
Chronic studies administered orally on compounds of Formula I and II were also conducted. The results showed that sub-threshold doses (10 and 20 mg/kg for the (R)-enantiomer) can produce as robust an anti-allodynic effect as an acute dose of compound I that is 10 fold higher. In contrast, the compound of Formula II demonstrated no anti-allodynic effect when tested chronically.

It has been shown that the compound of Formula I when administered orally to a mammal is metabolized to some extent to the compound of Formula II. This study clearly demonstrates that the anti-allodynic effects of the compound of Formula I do not arise as a result of the presence of compound II due to metabolization, but are a consequence of the anti-allodynic action of compound I. The levels of compound II found in the plasma after oral

administration of the (*R*)-enantiomer of Formula I was 5-10 fold less than that found after the oral administration of compound II itself.

Claims

1. A compound of the formula:



I

namely [2-(2,6-dimethylphenoxy)-1-methylethyl]ethylamine, or a pharmaceutically acceptable salt thereof.

2. The (R)-enantiomer of a compound of Claim 1, namely (R)-[2-(2,6-dimethylphenoxy)-1-methylethyl]ethylamine, or a pharmaceutically acceptable salt thereof.

3. The compound of Claim 2, wherein the pharmaceutically acceptable salt is (R)-[2-(2,6-dimethylphenoxy)-1-methylethyl]ethylamine hydrochloride.

4. The compound of Claim 2, wherein the pharmaceutically acceptable salt is (R)-[2-(2,6-dimethylphenoxy)-1-methylethyl]ethylamine tartrate.

5. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1, 2, 3 or 4, or a pharmaceutically acceptable salt thereof, in admixture with at least one pharmaceutically acceptable non-toxic carriers, particularly for the treatment of a mammal having a disease state which is alleviable by treatment with a sodium channel blocker, specially wherein the disease state is neuropathic pain.

6. The use of a compound of claim 1, 2, 3 or 4, for
the manufacture of a pharmaceutical composition for the
treatment of a mammal having a disease state which is
alleviable by treatment with a sodium channel blocker,
5 specially wherein the disease state is neuropathic pain.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 97/00135

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07C217/16 A61K31/13

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	US 3 659 019 A (KOPPE HERBERT ET AL) 25 April 1972 cited in the application see the whole document ---	1-6
-/--		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 97/00135

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